PATENT
ATTORNEY DOCKET NO.: 056291-0006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 5,770,599	)
Granted: June 23, 1998	)
Patentees: Kieth Hopkinson GIBSON	)
Assignee: Zeneca Limited	)
FOR: QUINAZOLINE DERIVATIVES	)

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop Patent Ext.**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: July 3, 2003

REQUEST FOR EXTENSION OF PATENT TERM
PURSUANT TO 35 U.S.C. § 156

Sir:

Applicant, AstraZeneca UK Limited, a corporation created and existing under the Laws of England and Wales, represents that it is the assignee of the entire interest in and to Letters Patent United States No. 5,770,599 granted to Kieth Hopkinson Gibson on June 23, 1998 for QUINAZOLINE DERIVATIVES, by virtue of an Assignment from the inventor thereof to ZENECA LIMITED, recorded April 26, 1996 at Reel 7973, Frame 0532 and an Assignment from ZENECA LIMITED to AstraZeneca UK Limited, a copy of that assignment with confirmation thereof having been filed for recordation on July 2, 2003, ZENECA LIMITED having changed its name to Syngenta Limited, the change of name certificate also having been filed for recordation on July 2, 2003. Pursuant to

 2004E-0398

APP 1

Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156(a), AstraZeneca UK Limited, hereby requests an extension of the patent term of U.S. Patent No. 5,770,599. A Revocation of Original Power of Attorney and Grant of New Power of Attorney was filed on July 2, 2003, authorizing the registered practitioners of Morgan, Lewis & Bockius LLP to act of behalf of Applicant, with correspondence and communications to be directed as set forth therein and in section (15) of this Application.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.710 *et seq.*; and follows the numerical sequence and format as set forth in 37 C.F.R. § 1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product is IRESSA®, which is further identified as follows:

Chemical Name:

4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-4-morpholin)propoxy] as set forth in the approved label insert, which also may be expressed by the nomenclature 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxyl] or 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline.

Generic Name:

Gefitinib

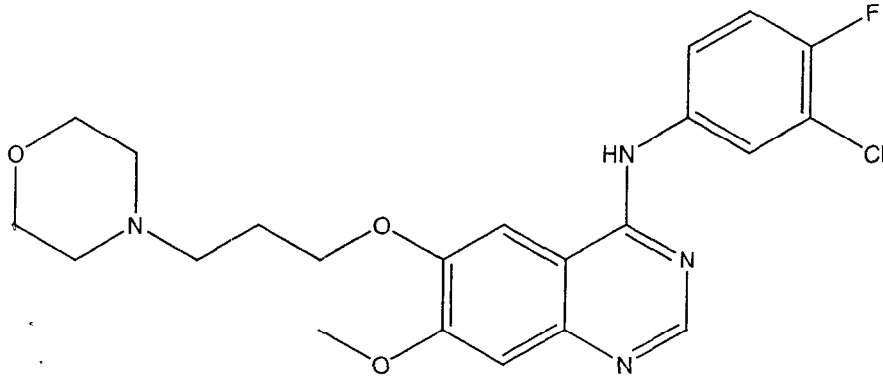
Molecular Formula:

$C_{22}H_{24}ClFN_4O_3$

Molecular Weight:

446.9

Structural Formula:



Gefitinib, as described above, is the active ingredient of the approved product IRESSA® as can be seen from **Exhibit 1**, being a copy of the approved labeling for the approved product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

IRESSA® was subject to regulatory review under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

IRESSA® received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(b)) upon approval of NDA 21-399 on May 5, 2003.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement

that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient of the product IRESSA® is gefitinib, which has not been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act prior to approval of NDA 21-399 on May 5, 2003.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved on May 5, 2003, and the last day within the sixty day period permitted for submission of an application for patent term extension is July 4, 2003.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

The complete identification of the patent for which an extension is being sought is as follows:

Inventor:	Kieth Hopkinson Gibson[1]
U.S. Patent No.:	5,770,599
Issue Date:	June 23, 1998
Expiration Date:	April 26, 2016

[1] It should be noted that the correct spelling of the inventor's first name is "Keith," as correctly set forth in the inventor's declaration and in the formal U.S. Patent and Trademark Office Filing Receipt. However, the erroneous spelling "Kieth" appears on the issued patent (apparently through a printing error), and therefore will be used herein for consistency with the printed patent.

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A full copy of U.S. Patent No. 5,770,599, for which extension is being sought, is attached as **Exhibit 2**.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

A copy of the maintenance fee statement showing timely payment of each maintenance fee when due is attached as **Exhibit 3**.

No disclaimer, certificate of correction or reexamination certificate has been filed and/or issued for U.S. Patent No. 5,770,599.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

- **(i) The approved product, if the listed claims include any claim to the approved product.**
- **(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and**
- **(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product;**

Claims of U.S. Patent 5,770,599 read on (i) the approved product and pharmaceutical compositions comprising the approved product, (ii) the method of using the approved product, and (iii) the method of manufacturing the approved product, as detailed below.

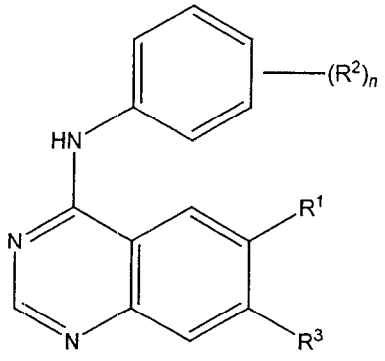
Claims to the Approved Product Include:

Claim 14 of U.S. Patent 5,770,599 specifically recites and reads on the approved product as follows:

> 14. The quinazoline derivative of the formula I as claimed in claim 1 being 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline;
>
> or a pharmaceutically-acceptable acid-addition salt thereof.

Generic product claim 1 reads as follows:

> 1. A quinazoline derivative of the formula I



I

> wherein
>
> n is 1, 2 or 3 and each R^2 is independently halogeno or trifluoromethyl
>
> R^3 is (1-4C)alkoxy; and
>
> R^1 is di-[(1-4C)alkyl]amino-(2-4C)alkoxy, pyrrolidin-1-yl-(2-4C)alkoxy, piperidino-(2-4C)alkoxy, morpholino-(2-4C)alkoxy, piperazin-1-yl-(2-4C)alkoxy, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy, imidazol-1-yl-(2-4C)alkoxy, di-[(1-4C)alkoxy-(2-4C)alkyl]amino-(2-4C)alkoxy, thiamorpholino-(2-4C)alkoxy, 1-oxothiamorpholino-(2-4C)alkoxy or 1,1-dioxothiamorpholino-(2-4C)alkoxy, and wherein any of the above-mentioned R^1 substituents comprising a CH_2 (methylene) group which is not attached to a N or O atom optionally bears on said CH_2 group a hydroxy substituent;
>
> or a pharmaceutically-acceptable salt thereof.

Generic product claim 1 reads on the approved product when n is 2; R^2 at the 3-position of the anilino ring is halogeno (chloro); R^2 at the 4-position of the anilino ring is halogeno (fluoro); R^3 is (1C)alkoxy; and R^1 is morpholino-(3C)alkoxy.

Generic product claim 2 reads as follows:

> 2. A quinazoline derivative of the formula I as claimed in claim 1 wherein n is 1, 2 or 3 and each R^2 is independently halogeno or trifluoromethyl;
>
> R^3 is (1-4C)alkoxy; and
>
> R^1 is di-[(1-4C)alkyl]amino-(2-4C)alkoxy, pyrrolidin-1-yl-(2-4C)alkoxy, piperidino-(2-4C)alkoxy, morpholino-(2-4C)alkoxy, piperazin-1-yl-(2-4C)alkoxy, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy, imidazol-1-yl-(2-4C)alkoxy or di-[(1-4C)alkoxy-(2-4C)alkyl]amino-(2-4C)alkoxy,
>
> and wherein any of the above-mentioned R^1 substituents comprising a CH_2 (methylene) group which is not attached to a N or O atom optionally bears on said CH_2 group a hydroxy substituent;
> or a pharmaceutically-acceptable salt thereof.

Generic product claim 2 reads on the approved product when n is 2; R^2 at the 3-position of the anilino ring is halogeno (chloro); R^2 at the 4-position of the anilino ring is halogeno (fluoro); R^3 is (1C)alkoxy; and R^1 is morpholino-(3C)alkoxy.

Generic product claim 3 reads as follows:

> 3. A quinazoline derivative of the formula I as claimed in claim 1 wherein $(R^2)_n$ is
>
> 3'-fluoro-4'-chloro or 3'-chloro-4'-fluoro;
>
> R^3 is methoxy; and
>
> R^1 is 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, 2-[di-(2-methoxyethyl)amino]ethoxy or 3-morpholino-2-hydroxypropoxy;
>
> or a pharmaceutically-acceptable mono- or di-acid-addition salt thereof.

Generic product claim 3 reads on the approved product when $(R^2)_n$ is 3'-chloro-4'-fluoro; R^3 is methoxy; and R^1 is 3-morpholinopropoxy.

Generic product claim 4 reads as follows:

> 4. A quinazoline derivative of the formula I as claimed in claim 1 wherein $(R^2)_n$ is 3'-chloro, 3'-bromo, 2',4'-difluoro, 2',4'-dichloro, 3',4'-difluoro, 3',4'-dichloro, 3'-fluoro-4'-chloro or 3'-chloro-4'-fluoro;
>
> R^3 is methoxy; and
>
> R^1 is 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 2-(imidazol-1-yl)ethoxy, 2-[di-(2-methoxyethyl)amino]ethoxy or 3-morpholino-2-hydroxypropoxy;
>
> or a pharmaceutically-acceptable acid-addition salt thereof.

Generic product claim 4 reads on the approved product when $(R^2)_n$ is 3'-chloro-4'-fluoro; R^3 is methoxy; and R^1 is 3-morpholinopropoxy.

Generic product claim 5 reads as follows:

> 5. A quinazoline derivative of the formula I as claimed in claim 1 wherein $(R^2)_n$ is 3'-chloro, 3'-bromo, 2',4'-difluoro, 2',4'-dichloro, 3',4'-difluoro, 3',4'-dichloro, 3'-fluoro-4'-chloro or 3'-chloro-4'-fluoro;
>
> R^3 is methoxy; and
>
> R^1 is 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 3-(pyrrolidin-1-yl)propoxy, 3-morpholinopropoxy or 3-morpholino-2-hydroxypropoxy;
>
> or a pharmaceutically-acceptable acid-addition salt thereof.

Generic product claim 5 reads on the approved product when $(R^2)_n$ is 3'-chloro-4'-fluoro; R^3 is methoxy; and R^1 is 3-morpholinopropoxy.

Generic product claim 6 reads as follows:

> 6. A quinazoline derivative of the formula I as claimed in claim 1 wherein $(R^2)_n$ is 3',4'-difluoro, 3',4'-dichloro, 3'-fluoro-4'-chloro or 3'-chloro-4'-fluoro;
>
> R^3 is methoxy; and
>
> R^1 is 3-morpholinopropoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

Generic product claim 6 reads on the approved product when $(R^2)_n$ is 3'-chloro-4'-fluoro.

Generic composition claim 17 reads as follows:

> 17. A pharmaceutical composition which comprises a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 15 in association with a pharmaceutically-acceptable diluent or carrier.

As described above, the approved product is encompassed within the scope of product claims 1-6 and 14 and additionally includes various pharmaceutically-acceptable diluents and/or carriers as set forth on the first page of **Exhibit 1**. For the reasons described above with respect to claims 1-6 and 14 upon which this claim is dependent, claim 17 reads on a pharmaceutical composition comprising the approved product.

Claim to Method of Using the Approved Product:

Method of using claim 18 reads as follows:

> 18. A method for producing an anti-proliferative effect in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 15.

The specification of U.S. Patent 5,770,599 discloses that "the compounds of the present invention are expected to be useful in the treatment of psoriasis and/or cancer by providing an anti-proliferative effect, particularly in the treatment of Class I receptor tyrosine kinase sensitive cancers such as cancers of the breast, lung, colon, rectum, stomach, prostate, bladder, pancreas and ovary" (col. 13, lines 47-53).

As set forth on page six of **Exhibit 1**, the approved product is indicated for the treatment of patients with non-small cell lung cancer. Therefore, for this reason and for

the reasons described with respect to claims 1-6 and 14 upon which this claim is dependent, claim 18 reads on a method of using the approved product.

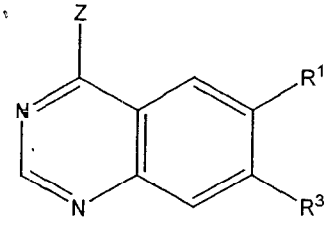
Claim to Method of Manufacturing the Approved Product:

Method of manufacturing claim 16 reads as follows:

16. A process for the preparation of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 15 which comprises

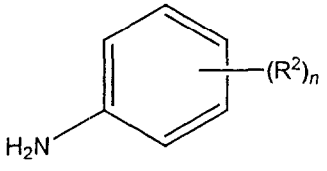
(a) the reaction of a quinazoline of the formula II

II



wherein Z is a displaceable group, with an aniline of the formula III

III



(b) for the production of those compounds of the formula I wherein R^1 is an amino-substituted (2-4C)alkoxy group, the alkylation of a quinazoline derivative of the formula I wherein R^1 is a hydroxy group;

(c) for the production of those compounds of the formula I wherein R^1 is an amino-substituted (2-4C)alkoxy group, the reaction of a compound of the formula I wherein R^1 is a hydroxy-(2-4C)alkoxy group, or a reactive derivative thereof, with an appropriate amine; or

(d) for the production of those compounds of the formula I wherein R^1 is a hydroxy-amino-(2-4C)alkoxy group, the reaction of a compound of the formula I wherein R^1 is a 2,3-epoxypropoxy or 3,4-epoxybutoxy group with an appropriate amine.

and when a pharmaceutically-acceptable salt of a quinazoline derivative of the formula I is required it may be obtained by reaction of said compound with a suitable acid using a conventional procedure.

The approved product may be made by any of processes (a), (b) and (c) in accordance with claim 16. The approved product may be described as a quinazoline derivative of the formula I wherein R^1 is a morpholino-(2-4C)alkoxy group. Pursuant to process (a), a quinazoline derivative of the formula I may be prepared by reacting a quinazoline of the formula II wherein R^1 is a morpholino-(2-4C)alkoxy group with an aniline of the formula III.

The approved product may also be described as a compound of the formula I wherein R^1 is an amino-substituted (2-4C)alkoxy group, namely R^1 is a morpholino-(2-4C)alkoxy group. Pursuant to process (b), alkylation of a quinazoline derivative of the formula I wherein R^1 is a hydroxy group may be used to prepare a compound of the formula I wherein R^1 is an amino-substituted (2-4C)alkoxy group, namely a compound wherein R^1 is a morpholino-(2-4C)alkoxy group.

Alternatively, pursuant to process (c), a compound of the formula I wherein R^1 is an amino-substituted (2-4C)alkoxy group, namely a morpholino-(2-4C)alkoxy group, may be prepared by the reaction of a compound of the formula I wherein R^1 is a hydroxy-(2-4C)alkoxy group, or a reactive derivative thereof, with an appropriate amine, namely with morpholine.

Therefore, for these reasons and for the reasons explained with respect to claims 1-6 and 14 upon which this claim is dependent, claim 16 reads on methods that may be used for manufacturing the approved product.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

The IND application for IRESSA® was submitted on November 17, 1997, and the IND became effective on December 17, 1997. By letter dated November 20, 1997, the FDA acknowledged receipt of the IND application on November 17, 1997, and assigned IND number 54,576. A copy of this letter is attached as **Exhibit 4**. This establishes the beginning of the "regulatory review period" under 35 U.S.C. 156(g)(1) as December 17, 1997.

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

The submissions constituting NDA Number 21-399 for IRESSA® began on July 30, 2001 and were completed on August 2, 2002. The final installment of the NDA submission was received by the FDA on August 5, 2002, as confirmed by **Exhibit 5**, which may be deemed to establish August 5, 2002 as the submission date of the NDA for the approved product for purposes of 35 U.S.C. 156(g)(1).[2]

---

[2] A rolling NDA procedure was used for the NDA submissions for IRESSA®. Without taking a position as to whether the NDA for IRESSA® was "initially submitted" upon FDA receipt of the initial installment or the final installment of the rolling NDA, the latter date has been used in this application inasmuch as the length of the extended term is, in either event, set by the 14 year limitation of 35 U.S.C. § 156(c)(3).

(C) The date on which the NDA was approved or the Product License issued.

The NDA was approved by the FDA approval letter sent May 5, 2003, setting the effective date of the approval as the May 5, 2003 date of the letter. A copy of this FDA approval letter is attached as **Exhibit 5.** This establishes the end of the "regulatory review period" under 35 U.S.C. 156(g)(1) as May 5, 2003.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

The regulatory activities undertaken to obtain approval of IRESSA® commenced with the submission of an Investigational New Drug Application (IND 54,576) on November 17, 1997 to study the use of gefitinib tablets (ZD1839) for the treatment of Epidermal Growth Factor Receptor (EGFR)-positive solid human tumors.

The testing phase of the regulatory review period consisted of activities occurring under IND 54,576. These activities included meetings with the FDA on January 10, 2000; April 6, 2000; July 29, 2000; January 16, 2001; May 18, 2001; June 14, 2001; November 21, 2001; December 13, 2001; December 19, 2001; January 18, 2002; April 23, 2002; and July 10, 2002; and timely submission of numerous documents required by regulation including Annual Reports on February 12, 1999; February 11, 2000; February 20, 2001; and January 16, 2002; Information Amendments, IND Safety Reports (initial and follow-up), New Protocols, and Protocol Amendments. In addition, many responses to FDA requests for information were promptly submitted.

Pursuant to Section 506(c) of the Federal Food, Drug, and Cosmetic Act, AstraZeneca began submitting installments of NDA 21-399 to the FDA during the testing phase. Installments were submitted on July 30, 2001; November 5, 2001; November 9, 2001; November 30, 2001; December 27, 2001; March 20, 2002; and July 3, 2002; and a 4-month Safety Update was submitted on May 23, 2002.

The testing phase ended and the approval phase of the regulatory review period began on August 5, 2002 when the FDA received the last installment of NDA 21-399. Many significant regulatory activities occurred during the approval phase, including meetings with FDA on September 5, 2002; October 4, 2002; October 15, 2002; October 18, 2002; November 20, 2002; January 6, 2003; January 13, 2003; January 17, 2003; January 23, 2003; February 6, 2003; February 13, 2003; March 17, 2003; March 27, 2003; April 8, 2003; and April 21, 2003; and an FDA Advisory Committee Meeting on September 24, 2002. In addition, numerous responses to FDA requests for information and revised draft labeling were timely submitted to the FDA during the approval phase.

The regulatory review period for IRESSA® ended with permission for commercial marketing being granted by FDA on May 5, 2003. All regulatory activities were carried out in a prompt, timely manner in accordance with all applicable statutes and regulations, reflecting the diligent pursuit of FDA approval of NDA 21-399 for IRESSA®.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

Statement That The Patent Is Eligible For Extension

Applicant is of the opinion that U.S. Patent 5,770,599 is eligible for extension under 35 U.S.C. 156(a) because it satisfies all of the requirements for such extension as follows:

(1) 35 U.S.C. 156(a)

U.S. Patent 5,770,599 claims the approved product, a method of using that product, and a method of manufacturing that product, as detailed in section (9) above.

(2) 35 U.S.C. 156(a)(1)

U.S Patent 5,770,599 granted on an earliest filed U.S. application filed on April 26, 1996 and there are no terminal disclaimers. As such, the patent expires on April 26, 2016. This application, therefore, has been submitted before the expiration of the patent term.

(3) 35 U.S.C. 156(a)(2)

The term of this patent has never been extended.

(4) 35 U.S.C. 156(a)(3)

This application is submitted by the owner of record in accordance with the requirement of 35 U.S.C. 156(d) and rules of the U.S. Patent and Trademark Office. AstraZeneca UK Limited is the owner of record of the patent through an assignment from the inventors to ZENECA LIMITED, recorded April 26, 1996 at Reel 7973, Frame 0532; and an assignment from ZENECA LIMITED to AstraZeneca UK Limited, a copy of that assignment with confirmation thereof having been filed for recordation on July 2, 2003 as evidenced by the

copy attached as **Exhibit 6**, ZENECA LIMITED having changed its name to Syngenta Limited, the change of name certificate having been filed for recordation on July 2, 2003 as evidenced by the copy attached as **Exhibit 7**.

(5) 35 U.S.C. 156(a)(4)

As evidenced by the May 5, 2003 approval letter from the FDA (**Exhibit 5**), IRESSA® was subject to a regulatory review period under Section 505(b) of the Federal Food, Drug, and Cosmetic Act before its commercial marketing or use.

(6) 35 U.S.C. 156(a)(5)(A)

The permission for commercial marketing of IRESSA® after this regulatory review period is the first permitted commercial marketing of IRESSA® under provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) under which the regulatory review period occurred, as confirmed by the absence of any approved NDA for the approved product prior to May 5, 2003.

(7) 35 U.S.C. 156(g)(4)

No other patent has been extended for the same regulatory review period for the product IRESSA®.

Statement as to Length of Extension Claimed

The term of U.S. Patent No. 5,770,599 should be extended by **374 days**, from April 26, 2016 to **May 5, 2017**. This extension is calculated on the following basis:

Title 35 U.S.C. 156(c) provides that the term of a patent eligible for extension under subsection (a) shall be extended by the time equal to the regulatory review period for the approved product which period occurs after the date the patent is issued, except that -- (1) each period of the regulatory review period shall be reduced by any period during which the applicant for the patent extension did not act with due diligence; (2)

after any such reduction required by paragraph (1), the period of extension shall include only one-half of the time remaining in the period under section 156(g)(1)(B)(i) (the testing period under an IND for a new drug); and (3) the total of the period of extension plus the period remaining in the term of the patent after the date of approval shall not exceed fourteen years. The "regulatory review period" is defined in section 156(g)(1), for a new drug product, as being the sum of (i) the testing period beginning on the date exemption under subsection (i) of section 505 (effective date of the IND) and ending on the date the NDA was initially submitted, and (ii) the approval period beginning on the date the NDA was submitted and ending on the date the NDA was approved. Section 156(g)(6) further provides that if the patent involved was issued after the date of the enactment of this section (September 24, 1984), then the period of extension may not exceed five years.

In context of the implementing regulations of 37 C.F.R. 1.175 with respect to patent term extensions for a human drug product, the term extension of U.S. Patent No. 5,770,599 based on the regulatory review for IRESSA® was determined as follows:

> **Sec. 1.775 Calculation of patent term extension for a human drug, antibiotic drug or human biological product.**
>
> **(a) If a determination is made pursuant to Sec. 1.750 that a patent for a human drug, antibiotic drug or human biological product is eligible for extension, the term shall be extended by the time as calculated in days in the manner indicated by this section. The patent term extension will run from the original expiration date of the patent or any earlier date set by terminal disclaimer (Sec. 1.321).**

U.S. Patent No. 5,770,599 was issued on June 23, 1998 from an earliest filed U.S. application filed on April 26, 1996. Pursuant to 35 U.S.C. 154(c), this patent is entitled to an original term of 20 years from April 26, 1996, which provides an original expiration date of April 26, 2016.

> **(b) The term of the patent for a human drug, antibiotic drug or human biological product will be extended by the length of the regulatory review period for the product as determined by the Secretary of Health and Human Services, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of this section.**

(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. 156(g)(1)(B), it is the sum of--

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the Public Health Service Act; and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days in the IND testing period of paragraph (c)(1) extends from the effective date of IND 54,576 on December 17, 1997 to the filing of NDA number 21-399 on August 5, 2002, being **1692 days**.

The number of days in the NDA approval period of paragraph (c)(2) extends from the filing of NDA number 21-399 on August 5, 2002 to the date of approval of NDA 21-399 on May 5, 2003, being **274 days**.

The regulatory review period is the sum of the periods of paragraphs (c)(1) and (c)(2), being **1966 days**.

(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by--

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1) (i) and (ii) of this section; half days will be ignored for purposes of subtraction;

With respect to paragraph (d)(1)(i), **188 days** of the periods of paragraphs (c)(1) and (c)(2) were before the June 23, 1998 date on which U.S. Patent 5,770,599 issued.

With respect to paragraph (d)(1)(ii), there were **no days** during which applicant did not act with due diligence during the periods of paragraphs (c)(1) and (c)(2), as detailed in section (11) above.

With respect to paragraph (d)(1)(iii), one-half of the number of days remaining in the period defined by paragraph (c)(1) after that period is reduced in accordance with paragraphs (d)(1) (i) and (ii) is one-half of 1504 days, which is **752 days**.

Subtracting from the regulatory review period of 1966 days as determined above pursuant to section 1.175(c) the number of days determined above with respect to paragraphs (d)(1) (i), (ii) and (iii), the term of patent extension is 1966 days minus 188 days minus 0 days minus 752 days for a sum total of **1026 days**.

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

The original term of U.S. Patent No. 5,770,599 is April 26, 2016 and is not shortened by terminal disclaimer. Adding the 1026 days determined in paragraph (d)(1) to the original term of the patent results in an extended term to **February 16, 2019.**

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to the May 5, 2003 date of the approval of the NDA results in a date **May 5, 2017**.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier of February 16, 2019 and May 5, 2017 is **May 5, 2017**.

(5) If the original patent was issued after September 24, 1984,
(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

The original patent was issued after September 24, 1984. Adding 5 years to the original expiration date of the patent (there was no terminal disclaimer) of April 26, 2016 gives a date of April 26, 2021. The earlier of April 26, 2021 and May 5, 2017 is **May 5, 2017**.

(6) If the original patent was issued before September 24, 1984, and
(i) If no request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act before September 24, 1984, by--
(A) Adding 5 years to the original expiration date of the patent or earlier date set by terminal disclaimer; and
(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(i)(A) of this section with each other and selecting the earlier date; or
(ii) If a request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, or Cosmetic Act before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, by--
(A) Adding 2 years to the original expiration date of the patent or earlier date set by terminal disclaimer, and
(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(ii)(A) of this section with each other and selecting the earlier date.

Since U.S. Patent No. 5,770,599 issued after September 24, 1984, no further adjustment to the extended term of May 5, 2017 is required.

Thus, as calculated above, the term of U.S. Patent No. 5,770,599 is eligible for a **374 day extension until May 5, 2017**.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see § 1.765).

Applicant acknowledges a duty to disclose to the Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (see § 1.20(j)).

As noted in the letter of transmittal submitted with this application, the Patent and Trademark Office is authorized to charge the filing fee of $1,120.00 and any additional fees which may be required by this or any other related paper, or to credit any overpayment to Deposit Account No. 50-0310.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

In accordance with the Revocation of Original Power of Attorney and Grant of New Power of Attorney filed on July 2, 2003 with respect to U.S. Patent No. 5,770,599 (copy attached as **Exhibit 8)**, please address all inquiries and correspondence relating to this application for patent term extension to:

Donald J. Bird
Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Telephone: 202-739-5320
Facsimile: 202-739-3001

Respectfully Submitted,
Morgan, Lewis & Bockius LLP

Date: July 3, 2003
Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:

By: _____
Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001